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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,907	06/05/2001	Jon A. Weidanz	49890(48340)	3602

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/874,907	WEIDANZ ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81,82,84-100,102-125 and 144-150* is/are pending in the application.

4a) Of the above claim(s) *84,87-100,103-123 and 125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81,82,85,86,102,124,144-150* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/19/08 has been entered.

2. Claims 81,82,85,86,102,124,144-150 are under consideration.

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.
The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration (the residence and PO address for Inventor Weidanz). See 37 CFR 1.52(c).
Applicant has indicated that a new declaration signed by Inventor Weidanz will be filed.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 81,82,85,86,102,124,144-150 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants arguments have been considered and deemed not persuasive.

a) There is no support in the specification as originally filed for the recitation of "alpha and beta variable chain covalently linked together by a second peptide linker" in claim 81.
The specification as originally filed does not disclose constructs containing only a Valpha and a Vbeta and also does not disclose such constructs linked by a peptide linker. The specification as originally filed discloses a variable alpha chain linked to a variable beta and Cbeta, but does not disclose a construct that lacks the Cbeta. The claims under consideration encompass TCR constructs without a Cbeta and such constructs are not disclosed in the specification as originally filed. Regarding applicants comments, the actual cited example to which applicant refers contains a Cbeta. The claims under consideration encompass TCR constructs without a Cbeta and such constructs are not disclosed in the specification as originally filed.

b) There is no support in the specification as originally filed for claim 144. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope in the context of any HLA molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

Regarding applicants comments, the cited passages of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope (aka other than the specific disclosed example) in the context of any HLA molecule (aka other than HLA 2.1). It also refers to toxin labeled molecules wherein cytokines are not toxins. The claims encompass TCR which bind any p53 peptide in the context of any HLA molecule whilst the specification only discloses a TCR which binds the specific peptide disclosed in the specification in the context of HLA 2.1. Applicant appears to be arguing that the limitation under consideration is obvious in view of a specific example disclosed in the specification, even though the specific example does not provide written description of the scope of the claimed invention. However, obviousness is not the

appropriate standard with regards to issues of written description. The CAFC stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1997) that:

3. Patentability/Validity -- Specification -- Written description (§ 115.1103)

Patent's entitlement to earlier filing date extends only to that which is disclosed in prior application, and does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed; one shows that one is "in possession" of invention of patent by describing invention, with all its claimed limitations, not that which makes it obvious, and although prior application need not describe claimed subject matter in exactly same terms used in claims, prior specification must contain equivalent description of claimed subject matter, and description which renders obvious invention for which earlier filing date is sought is not sufficient.

The CAFC also stated in Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir.
1977) that:

The invention is, for purposes of the 'written description' inquiry, whatever is now claimed ."") (emphasis in original). One does that by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. Although the exact terms need not be used in haec verba , see Eiselstein v. Frank , 52 F.3d 1035, 1038, 34 USPQ2d 1467, 1470 (Fed. Cir. 1995) (" [T]he prior application need not describe the claimed subject matter in exactly the same terms as used in the claims.. . ."), the specification must contain an equivalent description of the claimed subject matter. A description which renders obvious the invention for which an earlier filing date is sought is not sufficient.

c) There is no support in the specification as originally filed for claim 145. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope in the context of HLA 2.1 molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

Applicants arguments are as per addressed in b). There is no disclosure in the specification of the claimed molecule containing a cytokine which binds any p53 epitope

(aka other than the specific disclosed example) in the context of HLA 2.1 molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

d) There is no support in the specification as originally filed for claim 146. The cited passage of the specification/Examples refers to the p264 TCR which recognizes the specific sequence disclosed in the specification in the context of HLA 2.1. There is no disclosure in the specification of the claimed molecule containing a cytokine which contains any TCR which binds said p53 epitope in the context of any HLA molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

Applicants arguments are as per addressed in b). There is no disclosure in the specification of the claimed molecule containing a cytokine which contains any TCR which binds said p53 epitope in the context of any HLA molecule. It also refers to toxin labeled molecules wherein cytokines are not toxins.

e) There is no support in the specification as originally filed for the limitation of claim 147/148/149. The previously cited passage of the specification discloses said linkers between a TCR and a biologically active molecule, but does not disclose said linkers as used between an alpha and beta chain of a TCR.

Regarding applicants comments, the specification discloses said linkers between a TCR and a biologically active molecule, but does not disclose said linkers as used between an alpha and beta chain of a TCR. None of the examples cited by applicant disclose a linker consisting of ALA, SER and GLY connecting an alpha and beta TCR chains wherein said linker includes from about 8 to 16 amino acids. None of the examples cited by applicant disclose a construct with two linkers wherein the first and second linker encompass any peptides of about 7 to 20 amino acid. . None of the examples cited by applicant disclose a construct with two linkers wherein the first and second linker encompass any peptides of about 8 to 16 amino acid.
There is no support in the specification as originally for the scope of the claimed inventions (aka the claimed inventions constitute new matter).

The rejection of claim 149 for the reason elaborated in section f) of the previous Office

(There is no support in the specification as originally filed for the limitation of claim 149. The specification, page 19 discloses that "The linker is preferably predominantly comprises amino acids with small side chains, such as glycine, alanine and serine, to provide for flexibility.". Thus, the cited passage of the specification contains the additional limitation that the linker must provide for flexibility.) is withdrawn in view of the amended claim.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 81,82,85,86,102,124,144,145,147-150 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309). Applicants arguments have been considered and deemed not persuasive.

Weidanz et al. teach a soluble single chain alpha beta TCR wherein the Valpha and Vbeta chain are connected by a linker(see claims 1,2,4 and page 4, penultimate paragraph). The alpha beta chains of the TCR are covalently linked by the linker of claim 147 ((see page 24, last paragraph) wherein the optimal length would be determined via routine experimentation. The linker can contain the amino acids of claim

149 (see page 24, last paragraph). The TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 (see page 34, first paragraph). Weidanz et al. teach said TCR in a pharmaceutical (aka therapeutic) composition (see page 42). Weidanz et al. teach said TCR in a fusion protein containing an effector molecule wherein said effector is attached to the Valpha /Vbeta chain via an intervening Cκ or Cλ chain wherein said chain would function as a "peptide linker" (see claim 43). The "includes" of claim 148 is interpreted as equivalent in scope to "comprising". Weidanz et al. do not teach that the effector molecule is a cytokine. Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 3, lines 40-52 and column 2, last four paragraphs). Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). IL-2 is specific for recognition of an effector cells (immune cells expressing IL-2 receptor such as activated T cells). Bonneville et al. disclose that said TCR/IL-2 fusion proteins can be used to treat disease (see column 5, lines 57-60). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Weidanz et al. teach the claimed TCR fusion proteins except for use of IL-2 whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2. One of ordinary skill in the art would have been motivated to do the aforementioned because Weidanz et al. teach said TCR in a fusion protein containing an effector molecule whilst Bonneville et al. teach soluble TCR fusion proteins wherein a TCR is linked to IL-2 and that said TCR/IL-2 fusion proteins can be used to treat disease.

Regarding applicants comments about unpredictability of folding of cytokines, Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). The prior art is enabled in the absence of evidence to the contrary and no such evidence has been

provided by applicant. Regarding applicants comments about linker size, the only claim that actually specifies the length of the effector molecule/TCR linker molecule is claim 148/149. The "includes" of claim 148 is interpreted as equivalent in scope to "comprising" wherein the linker could therefore encompass additional amino acids.
Regarding applicants comments about Bonneville et al., Weidanz et al. teach a soluble single chain alpha beta TCR wherein the Valpha and Vbeta chain are connected by a linker(see claims 1,2,4 and page 4, penultimate paragraph). The alpha beta chains of the TCR are covalently linked by the linker of claim 147 ((see page 24, last paragraph) wherein the optimal length would be determined via routine experimentation. The linker can contain the amino acids of claim 149 (see page 24, last paragraph). Bonneville et al. teach a therapeutic composition containing soluble TCR fusion proteins wherein a TCR is linked to IL-2 (see column 5, lines 52-56). Bonneville et al. teach that the TCR can be a covalently linked single chain TCR containing alpha and beta chain variable regions (see abstract and column 2, penultimate paragraph). The prior art is enabled in the absence of evidence to the contrary and no such evidence has been provided by applicant. Regarding applicants reference to Ju et al., said publication is not of record and a copy has not furnished so applicants comments regarding said reference have not been considered.
Regarding the Wong declaration, there is no disclosure in said declaration of the actual structure of the constructs used or how they were made. Thus, it is unclear as to whether said constructs are encompassed by the claims under consideration and it is unclear if said constructs were made using methods disclosed in the specification. Thus, the relevance of the Wong declaration to the claimed invention is unclear.

8. Claim 146 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weidanz et al. (WO 99/18129) in view of Bonneville et al. (US Patent 5,723,309) as applied to claims 81,82,85,86,102,124,144,145,147-150 above, and further in view of Theobald et al. Applicants arguments have been considered and deemed not persuasive.

The previous rejection renders obvious the claimed invention except wherein the TCR binds the peptide of claim 146. Weidanz et al. disclose that the TCR can be

specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 (see page 34, first paragraph). Theobald et al. disclose HLA 2.1 antigen restricted CTL which contain TCR which bind the aformentioned peptide (see Table 1), where said CTL have the best lytic activity of the tested CTL (see Table 1). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except wherein the TCR binds the peptide of claim 146 whilst Weidanz et al. disclose that the TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 and Theobald et al. disclose antiP53 HLA 2.1 antigen restricted CTL which contain TCR which bind the aformentioned peptide (see Table 1), where said CTL have the best lytic activity of the tested CTL (see Table 1). One of ordinary skill in the art would have been motivated to do the aformentioned because Weidanz et al. disclose that the TCR can be specific for a single antigen such as P53 wherein the TCR recognizes said antigen in the context of HLA A2.1 and Theobald et al. disclose antiP53 HLA 2.1 antigen restricted CTL which contain TCR which bind the aformentioned peptide where said CTL have the best lytic activity of the tested CTL.

Applicants arguments are as per addressed above.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For

more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ron Schwadron/
Primary Examiner, Art Unit 1644